Complete Summary

GUIDELINE TITLE

Evaluation of surgery for Parkinson's disease. A report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. The Task Force on Surgery for Parkinson's Disease.

BIBLIOGRAPHIC SOURCE(S)

Hallett M, Litvan I. Evaluation of surgery for Parkinson's disease: a report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. The Task Force on Surgery for Parkinson's Disease. Neurology 1999 Dec 10;53(9):1910-21. [109 references]

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Parkinson's disease

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Evaluation
Technology Assessment

CLINICAL SPECIALTY

Neurological Surgery
Neurology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To review the role, safety, and indications of thalamotomy, pallidotomy, adrenal and fetal transplant, and deep brain stimulation in the treatment of Parkinson's disease

TARGET POPULATION

Patients with Parkinson's disease

INTERVENTIONS AND PRACTICES CONSIDERED

Neurosurgery

1. Thalamotomy (unilateral and bilateral)
2. Pallidotomy (unilateral and bilateral)
3. Deep brain stimulation of the ventral intermediate nucleus of the thalamus (unilateral and bilateral)
4. Deep brain stimulus of the globus pallidus
5. Deep brain stimulus of the subthalamic nucleus
6. Adrenal medullary transplants
7. Human fetal mesencephalic cell transplants

Imaging and mapping procedures for radiologic and physiologic localization

1. Computed tomography (CT) targeting
2. Magnetic resonance imaging (MRI) targeting
3. Macroelectrode stimulation mapping and microelectrode recording/stimulation mapping
4. Positron emission tomography

MAJOR OUTCOMES CONSIDERED

- Degree of tremor control
- Motor performance, as measured by rate of contralateral drug-induced dyskinesia, bradykinesia, and scores on the Unified Parkinson Disease Rating Scale (UPDRS) and Core Assessment Protocol for Intracerebral Transplantation (CAPIT)
- Measures of activities of daily living, including degree of disability
- Levodopa dosage reductions
- Surgical complications and adverse effects

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

This study was based on a Medline, Embase, and Biosis bibliographic search from 1991 through 1998. The terms used for the search included: parkinsonism or PD and pallidotomy or thalamotomy or thalamus surgery, globus pallidus surgery, or subthalamic nucleus surgery; brain stimulation or electrostimulation or electrical stimulation; cell transplantation or cell transplant or tissue transplant or tissue transplantation; and therapy as a modifier. Articles selected for evaluation by each working group had at least four patients, except for studies on fetal transplantation and deep brain stimulation of the globus pallidus and subthalamic nucleus, which required at least two patients because studies with at least four patients were limited.

NUMBER OF SOURCE DOCUMENTS

Articles identified through searches

18 for thalamotomy

40 for pallidotomy

38 for deep brain stimulation of the thalamus

10 for deep brain stimulation of the globus pallidus

6 for deep brain stimulation of the subthalamic nucleus

52 for adrenal medullary transplantation

19 for human fetal mesencephalon transplantation

Articles meeting inclusion criteria

4 for thalamotomy

22 for pallidotomy

16 for deep brain stimulation of the thalamus

10 for deep brain stimulation of the globus pallidus

6 for deep brain stimulation of the subthalamic nucleus

9 for adrenal medullary transplantation

19 for human fetal mesencephalon transplantation

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Classes of evidence

Class I: Evidence provided by one or more well-designed randomized controlled clinical trials.

Class II: Evidence provided by one or more well-designed clinical studies such as prospective open, case-controlled studies, etc.

Class III: Evidence provided by expert opinion, non-randomized historical controls, or case reports of one or more patients.

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Citations were identified then evaluated by at least two members of each working group, who read the whole article and made the decision to include or exclude according to American Academy of Neurology guidelines as well as CONSORT guidelines.

Each working group classified each paper based on the type of evidence it provided. Almost all papers finally included were Class III (see "Rating Scheme for the Strength of the Evidence" in this summary or Appendix 2 in the guideline document for definitions), peer reviewed, used validated methods of assessment, and provided consistent clinical (rather than technical) data. Although most studies considered were prospective, only two included a concurrent control group, a requirement necessary to meet Class II evidence.

Once the evidence regarding all the articles reviewed was classified, each working group summarized all the collected data and indicated the quality of the evidence of all citations contributing to their recommendations.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

The Possible Strengths of Recommendations.

Type A: Strong positive recommendation, based on Class I evidence or overwhelming Class II evidence when circumstances preclude randomized clinical trials.

Type B: Positive recommendation, based on Class II evidence.

Type C: Positive recommendation, based on strong consensus of Class III evidence.

Type D: Negative recommendation, based on inconclusive or conflicting Class II evidence or consensus of Class III evidence.

Type E: Strong negative recommendation, based on evidence of ineffectiveness or lack of efficacy, based on Class I or Class II evidence.

Possible Recommendations.

Safe: A judgment of the acceptability of risk in a specified situation, e.g., for a given medical problem, by a provider with specified training, at a specified type of facility.

Effective: Producing a desired effect under conditions of actual use.

Established: Accepted as appropriate by the practicing medical community for the given indication in the specified patient population.

Possibly useful: Given current knowledge, this technology appears to be appropriate for the given indication in the specified patient population. If more experience and long-term follow-up are accumulated, this interim rating may change.

Investigational: Evidence insufficient to determine appropriateness, warrants further study. Use of this technology for given indication in the specified patient population should be confined largely to research protocols.

Doubtful: Given current knowledge, this technology appears to be inappropriate for the given indication in the specified patient population. If more experience and long-term follow-up are accumulated, this interim rating may change.

Unacceptable: Regarded by the practicing medical community as inappropriate for the given indication in the specified patient population.

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

A draft of the guideline document was circulated among all the study participants for their final review and comments.

The guideline was approved by the American Academy of Neurology Therapeutics and Technology Subcommittee on July 9, 1999, by the Practice Committee on July 10, 1999,and by the Executive Board of the American Academy of Neurology on October 2, 1999.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Each procedure includes a ranking for the quality of evidence supporting it, as well as a rating of the strength of the recommendation, when appropriate. Definitions of the levels of evidence (I-III) and the strength of recommendation (A-E), as well as a glossary of possible recommendation terms are provided at the end of the Major Recommendations field.

Thalamotomy

Indications and technical components

Thalamotomy directed to the ventral intermediate nucleus is indicated for asymmetric, severe, medically intractable tremor, particularly when the tremor is not associated with important symptoms from other features of Parkinson's disease. Data collection was retrospective (Class III). Thalamotomy is not effective for treatment of bradykinesia, micrographia, or difficulty with gait or speech, but targeted to the ventral oral posterior nucleus it may have value for rigidity and dyskinesia. The authors emphasize the operation directed to the ventral intermediate target in the guideline document.

Thalamotomy on the second side has a good chance at decreasing tremor but a high incidence of speech problems. Therefore, if surgery is considered, ventral intermediate-deep brain stimulation is the treatment of choice for the second side.

The operation is generally not appropriate for atypical parkinsonism, including multiple system atrophy, but in the rare patient with severe disabling tremor, thalamotomy might be beneficial.

Two studies employed computed tomography scanning for at least part of the study and the same two employed microelectrode or semi-microelectrode recording for physiologic localization. These methods seem important for proper localization within the thalamus, but controlled observations on this point are not available.

Recommendation

It is recommended that thalamotomy be offered to the Parkinson's disease patient for surgical treatment of asymmetric, severe, and medically intractable tremor, but not for bradykinesia or difficulty with gait or speech. For this purpose, thalamotomy is reasonably safe and effective, with a type C recommendation

based on Class III evidence. Contraindications include atypical parkinsonism, multiple system atrophy, and high surgical risk from medical disease. Computerized imaging should be employed for radiologic localization and microelectrode recording for physiologic localization is likely helpful. Thalamotomy is an option for operation of the second side if the patient is willing to accept the possibility of dysarthria, but because of this significant risk, bilateral thalamotomy would have to be considered doubtful-a type D recommendation based on minimal evidence. If an operation on the second side is desirable, then deep brain stimulation of the thalamus may well be the treatment of choice because it can be better controlled, but there are no published data to support this view.

Pallidotomy

Indications and technical components

Unilateral pallidotomy is indicated for advanced Parkinson's disease with motor fluctuations and drug-induced involuntary movements (dyskinesias) along with significant bradykinesia and rigidity, with or without tremor. The improvements in these cardinal features of Parkinson's disease last at least 2 years, as documented by following a total of 22 patients from two studies. The effects and duration of benefit of unilateral pallidotomy on gait and postural disturbances are less striking. Because of the risks associated with the surgery and the unknown long-term benefit, pallidotomy should be offered to patients who continue to have significant motor disability interfering with normal activities of daily living despite optimal medications. The magnitude of the improvement appears to be greatest for drug-induced dyskinesias. There is the suggestion that responsiveness to levodopa should be a criterion for inclusion. There is also evidence that hypermetabolism in the globus pallidus as assessed by fluoro-deoxyglucose uptake in the pallidal complex is a predictor of a beneficial response to pallidotomy. Symptoms persisting in the "on" state (e.g., freezing, falls, dysarthria) do not respond well to pallidotomy. Benefits are predominantly contralateral, suggesting that asymmetric patients stand to improve the most with pallidotomy.

There are insufficient reliable data on the indications, safety, or benefits of bilateral pallidotomy. The available data, however, suggest that bilateral pallidotomy is associated with a higher incidence of neurologic adverse effects, particularly speech complications.

Preliminary evidence from some of the groups who have published the evaluable studies indicates that patients with other parkinsonian disorders failing to respond to levodopa do not substantially benefit from pallidotomy.

Computed tomography or magnetic resonance imaging targeting is most widely used. All papers evaluated in the guideline document used physiologic mapping in addition to aid in target selection. Both macroelectrode stimulation mapping and microelectrode recoding/stimulation mapping are being used. It is impossible to assess which imaging or mapping procedure is superior with the available data. Microelectrode recording mapping requires more equipment and experienced personnel. A study comparing the benefits and adverse effects of pallidotomy using microelectrode versus macroelectrode mapping is not available.

Studies utilizing radiosurgical, nonphysiologically guided pallidotomy (gamma knife) could not be adequately evaluated. Whereas there is one report of comparable benefit to radiofrequency lesioning, others report limited benefits and substantial complications. Thus, this method cannot be recommended at the present time as standard care.

Although the posterior ventral portion of the internal division of the globus pallidus is the common target, there is not yet certainty of the optimal target.

Recommendation

Based on the authors' survey, unilateral pallidotomy is safe and effective with a Type C recommendation (positive recommendation based on Class III evidence). Unilateral pallidotomy is recommended for patients with Parkinson's disease with bradykinesia, rigidity, and tremor who experience significant drug-induced dyskinesia. The greatest benefit seems to be in ameliorating the dyskinesia. There is less benefit to gait and postural disturbance than other features of Parkinson's disease. The ideal candidate is young, cognitively intact, has asymmetric disease with dyskinesias, and is responsive to levodopa (L-DOPA). The benefits of pallidotomy are maintained for at least 2 years; further long-term follow-up is required. Pallidotomy requires considerable expertise in stereotactic and functional neurosurgery. Physiologic mapping with either microelectrode recordings and stimulation or macroelectrode stimulation may improve the results. Although the optimal lesion location and volume are yet to be determined, there is increasing evidence that precise lesion placement within the internal segment of the globus pallidus is critical and that lesions outside this area are less effective. Because little data on the cognitive consequences of pallidotomy are available, it is recommended that patients undergo a pre- and post-operative neuropsychological assessment. The benefits of pallidotomy are predominantly contralateral.

No reliable data are available on the indication, safety, or efficacy of bilateral pallidotomy. Preliminary reports, however, suggest a high incidence of speech complications with bilateral pallidotomy. Bilateral procedures may carry significant risk and would have to be considered doubtful, with type D negative recommendation based on minimal data.

Deep Brain Stimulation of the Ventral Intermediate Nucleus of the Thalamus

Indications and technical components

The indication for high-frequency stimulation of the ventral intermediate thalamic nucleus is severe and disabling tremor that is unresponsive to medical therapy. Good candidates for the procedure are patients with functional disability due to tremor and not to other motor symptoms such as bradykinesia. Rest, postural (proximal and distal), and kinetic tremor improve with deep brain stimulation; improvement in disability correlates with improvement in postural tremor. Most experience has been in patients with Parkinson's disease or essential tremor, although other miscellaneous tremors related to midbrain and cerebellar disease have also been studied.

Tremor may not be well controlled pharmacologically in 20 to 30% of Parkinson's disease patients. However, because for most of these patients the tremor is not the major cause of disability, they are not candidates for thalamic deep brain stimulation. This leaves a small group of patients (<5%) who may be suitable for surgery.

Severe bilateral tremor may be an indication for bilateral procedures-either thalamotomy on one side followed by deep brain stimulation on the other or bilateral deep brain stimulation. Owing to its low morbidity, deep brain stimulation of ventral intermediate can be performed bilaterally in patients with severe bilateral tremor, often during one surgical session.

Dementia is a relative contraindication because the patient must be able to cooperate in the operating room and because dementia may be exacerbated by any further brain disturbances. Age, per se, is not a contraindication and the procedure has been performed in patients up to 81 years of age. Activities in certain occupations may induce the repetitive turning on and off of the device and may contraindicate this procedure.

A stereotactic frame is attached to the patient's head under local anesthesia. The ventral intermediate nucleus of the thalamus is targeted by various methods using computed tomography and magnetic resonance imaging localization. In the operating room, a burr hole is made under local anesthesia. The electrode is advanced to the ventral intermediate under stereotactic guidance. Stimulation through the electrode is used to find the site that produces the best suppression of tremor with the least paresthesias or other unwanted side effects. The final position of the electrode tip is selected to provide maximum tremor suppression at the lowest stimulation intensity with only transient paresthesia in the arm and face at the initiation of stimulation. At the time of surgery or several days later, the impulse generator is placed in the subcutaneous tissue of the infraclavicular area, connected subcutaneously by an extension wire to the implanted electrode, and programmed to yield the greatest tremor suppression with the least side effects. Other groups use microrecording first in order to localize the optimal site for macroelectrode implantation. In essence, the size of the affected region and location may be specified by modifying stimulation parameters. Stimulation parameters and contact selection are programmed by telemetry. The adjustable parameters include contact selection (with quadripolar electrodes), pulse rate, pulse width, and pulse amplitude. Patients are able to switch their impulse generator on or off by means of a hand-held magnet, but cannot alter the settings.

The procedure can be done bilaterally, in either one or two sessions.

Deep brain stimulation of the thalamus is effective only in reducing parkinsonian tremor and does not affect bradykinesia. For this reason, there is much interest in stimulation of the globus pallidus interna and the subthalamic nucleus in an effort to control the other symptoms of Parkinson's disease as well as the tremor.

One member of the team must become familiar with programming the impulse generator and adjusting the stimulation parameters for optimal response. Programming the stimulator is very time-consuming in the first few months for

some patients, and is an ongoing problem in others. Continuing surveillance is needed, and the impulse generator needs to be changed every 3 to 5 years.

Recommendations

Deep brain stimulation of the thalamus for tremor in Parkinson's disease patients is rated as safe and effective with a type C recommendation based on Class III evidence. Bilateral thalamic deep brain stimulation appears safe and effective also, but remains investigational as there are only limited data.

Deep Brain Stimulation of the Globus Pallidus

Indications and technical components

Virtually all patients selected for surgery in reported studies had advanced disease, Hoehn and Yahr stages 3 and 4, with associated motor fluctuations and dopa dyskinesias. Two patients had multiple system atrophy. There are no formal discussions of contraindications, but most patients have been in reasonably good health and not cognitively impaired.

The technical aspects are similar to those reported in the prior discussion of deep brain stimulation of the thalamus and will not be repeated here. Considerable time is needed to optimize the programming of the device.

Recommendations

Results are largely favorable, and complications are typically transient. The targeted group is patients with severe Parkinson's disease with fluctuations and dyskinesias. There are only limited data reported for other parkinsonian states, but for multiple system atrophy, at least, the procedure does not seem indicated. The indications are much the same as for pallidotomy, and the considerations of the choice between pallidotomy and deep brain stimulation of the pallidum is similar to that of the choice between thalamotomy and deep brain stimulation of the thalamus. However, another alternative is deep brain stimulation of the subthalamic nucleus. There has been one report comparing the efficacy of the two targets, and this has suggested that deep brain stimulation of the subthalamic nucleus is more effective. Because the indications for deep brain stimulation of the pallidum are, therefore, not certain, the procedure is best considered still investigational.

Deep Brain Stimulation of the Subthalamic Nucleus

Indications and technical components

Although this procedure is being widely done, only two groups, from Grenoble and Toronto, have reported their results in the peer-reviewed literature. Indications have been limited to patients with severe Parkinson's disease with fluctuations. Dyskinesias, although originally not considered an indication, are now included. All cases have been done bilaterally. Most patients have been in reasonably good health and not cognitively impaired, and there is a suggestion that older patients might not do as well.

The technical aspects are similar to those reported in the prior discussion of deep brain stimulation of the thalamus and will not be repeated here. Considerable time is needed to optimize the programming of the device. In comparison with the globus pallidus, the subthalamic nucleus is a smaller target.

Recommendations

There is insufficient experience reported to date with deep brain stimulation of the subthalamic nucleus to come to a definite conclusion, and it must be considered still investigational. The beneficial effects for all aspects of Parkinson's disease are impressive, but there are a number of complications that have occurred. Most complications have been transient or mild, but some have been significant, and this will have to be weighed against the possible benefit. As noted above, the risk for younger patients may be significantly less. There seems to be considerable enthusiasm for this procedure, particularly in Europe, where it has already been approved for the treatment of Parkinson's disease, and new results will be appearing soon that may allow a positive recommendation.

In relation to approaches to the subthalamic nucleus, subthalamotomy is also being investigated in a few centers and preliminary results have been reported.

Adrenal Medullary Transplants

Indications and technical components

The studies focused on patients with idiopathic Parkinson's disease who were increasingly unresponsive to medication and who had motor fluctuations. Patients were examined to identify that they had two adrenal glands preoperatively. In all cases, the operation was performed once and not repeated on the other side. Contraindications were patients without two adrenal glands and those without clinically definite Parkinson's disease.

The prototypic surgery involved an adrenalectomy, either abdominal or retroperitoneal, and a simultaneous craniotomy with transplantation of dissected adrenal medullary tissue into one (usually right-sided) caudate nucleus (i.e., into the nondominant hemisphere). Some studies used an open frontal craniotomy and others used stereotaxic guidance.

Three ideas for modified protocols have evolved from these studies: first, special perfusion techniques aimed at increasing cell survival; second, the addition of trophic factors or peripheral nerve cotransplants to enhance cell survival; and third, the grafting of fetal adrenal medullary cells. Cotransplantation procedures combining adrenal medullary tissue with peripheral nerve fragments have been performed in two small series (<5 subjects each), and in each, selected patients improved.

The primary problem with adrenal surgery was the double procedure, abdominal and cerebral, involving two teams, long intraoperative time, and long recovery. Morbidity was less with retroperitoneal surgery than frontal-abdominal and less with stereotaxic than open craniotomy. Surgical and perisurgical complications included pulmonary, abdominal, psychiatric, and neurologic, and late sequelae

included persistent hemiparesis, seizures, and behavior disinhibition in some patients.

These studies were all begun before the development of the Core Assessment Protocol for Intracerebral Transplantation (CAPIT), so there were individual variations in the scale selected.

No assessments were blinded.

Recommendation

Based on the cited studies, adrenal medullary transplant in Parkinson's disease appears to be a difficult double operation procedure when performed on severely advanced Parkinson's disease patients. Most studies suggested efficacy but morbidity was high. There have been no controlled studies. At the current time, the procedure should be considered unacceptable for safety reasons. The quality of the data is Class III, and the strength of the recommendation is Type D.

To the committee's knowledge, the procedure is not being currently investigated further.

Human fetal mesencephalic cell transplants

Indications and technical components

The studies focused on patients with idiopathic Parkinson's disease who were poorly controlled with medication and who had motor fluctuations. Patients with secondary parkinsonism from toxin exposure with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) or other degenerative conditions are not considered in the guideline report. In most series, the numbers were relatively small, ranging from 2 to 12. In most patients, immunosuppression was used for varying periods of time pre- and post-operatively. In unilateral cases, one operation was performed. With the bilateral procedures, staging of operations with intervals approximating 1 to 3 weeks was usual. Follow-up ranged from 6 months to 5 years.

In most instances, significant other medical illnesses precluded entry into the study. Some groups had age restrictions.

Whereas in the adrenal transplants there were basically two types of adrenalectomy and two types of cranial surgery, the number of variables is much larger with fetal transplantation. In terms of the tissue preparation, there are two principal choices, either dissection of blocks of tissue or creation of a suspension of dissociated cells. Usually the donor (i.e., the mother) is screened for human immunodeficiency virus (HIV)-I; HIV-II; human T-cell leukemia virus-1(HTLV-1); hepatitis A, B, and C; cytomegalovirus; toxoplasmosis; syphilis; and herpes simplex virus. In addition, fetal tissue is cultured for aerobic and anaerobic bacteria, yeast, herpes simplex virus, and cytomegalovirus. Not much testing can be done on the fetus, because there is such a short period of time available. Dopamine production is assessed by a few teams, but cooling of the tissue (a necessary technical aspect) slows metabolism and gives a false reading. Viability

testing by trypan blue staining is more standard. Other variables are donor age, immunosuppression, and tissue storage techniques. Open or stereotaxic surgery can be used, although open surgery is usually unilateral and stereotaxic procedures can be either unilateral or bilateral. The site of transplantation varied among studies, focusing on caudate nucleus, putamen, or both. Within the putamen itself, investigators differed in placing the transplant diffusely or aiming selectively to the anterior or posterior putamen. Likewise, donor tissue age varied from 5 to 17 weeks postconception. Basic science studies suggest that tissue older than 10 weeks has largely differentiated and already sent out neuritic processes. This maturation prior to transplant reduces survival of cells and integration with host tissue in experimental animals. Additionally, the number of mesencephalons transplanted has varied from one to four per side, making the full range in unilateral and bilateral cases from one to eight. Finally, the issue of immunosuppression is not uniform in these studies, some having none at all, some having only cyclosporin for short periods, and others having more complete and more protracted treatment.

With the number of potential technical variables, protocols to test the effect of each one could be envisioned. However, in the United States, a significant difficulty with implementation has been the political and ethical pressures against such research efforts. The limitation of available human fetal tissue in North America and Europe suggests that large-scale evaluations of each possible operative variable will not likely occur. For the future, other possible cell sources, such as porcine xenografts, and engineered cells are being investigated.

All included studies used standardized rating scales to measure outcomes. These studies primarily used the Unified Parkinson Disease Rating Scale and assessed motor fluctuations. Some used the Core Assessment Protocol for Intracerebral Transplantation, which includes responses to a standard L-DOPA dose. Two studies focused on psychometric changes and used standard scales for these measures. Positron emission tomography scanning was used in approximately half of the groups, but data were often incomplete and performed only on a subsample.

Recommendations

Based on the cited Class III studies, human fetal transplantation into the striatum in Parkinson's disease appears to be an encouraging procedure when performed on severely advanced Parkinson's disease patients. Because of the absence of controlled studies, it is investigational as a procedure for advanced Parkinson's disease at a research center. It is promising, because its efficacy appears to be good in the published reports, and its associated morbidity and mortality are low. Further modifications in surgical, dissection, and preservation techniques; the possibility of supplementation with trophic factors; or combination with other neurosurgical procedures such as pallidotomy and thalamotomy are areas of future potential research with controlled studies. Several prospective controlled trials are currently in progress, and further data should be available soon.

Conclusions

Surgery for Parkinson's disease is rapidly becoming an important therapeutic consideration in the management of medication-resistant disease (see table

below), based on a strong consensus of Class III evidence (i.e., provided by nonrandomized, historical controls or case series). In carefully selected cases, thalamotomy and deep brain stimulation of the thalamus can safely and effectively control tremor. It is clear, however, that they cannot help bradykinesia, which typically is, or will become over time, the most important symptom. Hence, other procedures should always be considered even if tremor is the main symptom. When the problem is severe dyskinesias and on-off fluctuations, unilateral pallidotomy has been demonstrated to be effective and reasonably safe. For bilateral pallidotomy, the risks are substantial, limiting its potential utility. Pallidal deep brain stimulation may well be demonstrated to be a good alternative, and it can be done bilaterally more safely. The influence of pallidal surgery on bradykinesia, however, seems limited, at least when compared to the levodopa-induced "on" state. For improvement of bradykinesia, fetal implantation surgery seems promising, but remains investigational. Implantation with other types of cells, including engineered cells, will be employed in the future. Adrenal implantation surgery has been abandoned. For bradykinesia, deep brain stimulation of the subthalamic nucleus, typically done bilaterally, appears very promising, although it too is currently investigational. Other considerations are that procedures such as thalamotomy and pallidotomy are immediate in effect and essentially complete at the time of operation, but irreversible. deep brain stimulation makes no major lesion, but requires intensive postoperative adjustments and lifelong maintenance. Implants are not immediate in their effect and may require immunosuppression. In making a decision about any type of surgery, the risks should be weighted against any possible benefit. Because these procedures are under intense investigation, new knowledge is expected to accrue rapidly and the recommendations concluded here will evolve.

Table - Summary of Recommendations*

Procedure	Bradykinesia	Tremor	Dyskinesia	Recommendation	Strength of recommendation
Unilateral thalamotomy	No	Yes	No	Safe, effective	C
Bilateral thalamotomy	No	Yes	No	Doubtful	D
Unilateral pallidotomy	Yes	Yes	Yes	Safe, effective	C
Bilateral pallidotomy	Yes	Yes	Yes	Doubtful	D
Unilateral deep brain stimulation thalamus	No	Yes	No	Safe, effective	C
Bilateral deep brain	No	Yes	No	Investigational	

stimulation thalamus					
Deep brain stimulation pallidumâ	Yes	Yes	Yes	Investigational	
Deep brain stimulation subthalamic nucleusâ	Yes	Yes	Yes	Investigational	
Adrenal implant	Yes	Yes	Yes	Unacceptable	D
Fetal implant	Yes	Yes	Yes	Investigational	

* A yes or no in the bradykinesia, tremor, or dyskinesia column reflects whether the procedure affects these symptoms.

â Deep brain stimulation of the pallidum and subthalamic nucleus is typically done bilaterally.

Definitions:

Classes of Evidence

Class I: Evidence provided by one or more well-designed randomized controlled clinical trials.

Class II: Evidence provided by one or more well-designed clinical studies such as prospective open, case-controlled studies, etc.

Class III: Evidence provided by expert opinion, non-randomized historical controls, or case reports of one or more patients.

Possible Strengths of Recommendations

Type A: Strong positive recommendation, based on Class I evidence or overwhelming Class II evidence when circumstances preclude randomized clinical trials.

Type B: Positive recommendation, based on Class II evidence.

Type C: Positive recommendation, based on strong consensus of Class III evidence.

Type D: Negative recommendation, based on inconclusive or conflicting Class II evidence or consensus of Class III evidence.

Type E: Strong negative recommendation, based on evidence of ineffectiveness or lack of efficacy, based on Class I or Class II evidence.

Possible Recommendations

Safe: A judgment of the acceptability of risk in a specified situation, e.g., for a given medical problem, by a provider with specified training, at a specified type of facility.

Effective: Producing a desired effect under conditions of actual use.

Established: Accepted as appropriate by the practicing medical community for the given indication in the specified patient population.

Possibly useful: Given current knowledge, this technology appears to be appropriate for the given indication in the specified patient population. If more experience and long-term follow-up are accumulated, this interim rating may change.

Investigational: Evidence insufficient to determine appropriateness, warrants further study. Use of this technology for given indication in the specified patient population should be confined largely to research protocols.

Doubtful: Given current knowledge, this technology appears to be inappropriate for the given indication in the specified patient population. If more experience and long-term follow-up are accumulated, this interim rating may change.

Unacceptable: Regarded by the practicing medical community as inappropriate for the given indication in the specified patient population.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for each recommendation (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Thalamotomy

In carefully selected cases, thalamotomy can safely and effectively control asymmetric, severe, and medically intractable tremor.

Pallidotomy

Unilateral pallidotomy is effective and reasonably safe for advanced Parkinson's disease with motor fluctuations and drug-induced involuntary movements (dyskinesias) along with significant bradykinesia and rigidity, with or without tremor. The improvements in these cardinal features of Parkinson's disease have lasted at least 2 years. Improvements include: marked amelioration of contralateral drug-induced dyskinesias, reaching over 90%; total Unified Parkinson Disease Rating Scale and contralateral scale motor improvements in the "off" state of approximately 30%; and substantial decrease in contralateral tremor score of approximately 50 to 60%. In addition, measures of activities of daily living improve in both the "on" and "off" states with unilateral pallidotomy.

Deep brain stimulation of the ventral intermediate nucleus

Some patients have an immediate response even without stimulation through the implanted electrode. Brain stimulation of the ventral intermediate nucleus has proved effective in reducing contralateral tremor for up to 8 years. Some patients have had complete tremor resolution, and more than 80% of patients report a significant reduction on tremor contralateral to stimulation.

Deep brain stimulation of the globus pallidus

There are benefits to all aspects of parkinsonism including bradykinesia, speech, walking, rigidity, and tremor. Particularly dramatic is the marked reduction in dyskinesias. There is clear antiparkinsonian effect seen in the drug off state.

Deep brain stimulation of the subthalamic nucleus

Patients improved substantially in all aspects, including tremor, akinesia, postural stability, and gait. There was a 60% improvement in motor score and score for activities of daily living in the "off" states before surgery and with deep brain stimulation post-operatively. There was a 10% improvement in the "on" states, but the time spent in the "on" state was markedly increased. There was significant improvement in both the intensity and duration of dyskinesias, and the painful "off"-period dystonia disappeared or diminished.

Human fetal mesencephalic cell transplantation

Motor performance, including improved function during the off state and more hours of on time, occurred in some of the patients. Doses of levodopa (L-DOPA) were reduced in some cases. Improvement generally started after 3 to 6 months and lasted up to 5 years.

Subgroups Most Likely to Benefit:

Pallidotomy

The bulk of the data suggest that younger patients derive more benefit from pallidotomy than older patients. The choice of pallidotomy for young patients, however, has to be balanced with the uncertainty of the long-term consequences

of the procedure and the possibility that surgery may diminish therapeutic benefits of future medical or surgical treatments.

POTENTIAL HARMS

Thalamotomy

Transient complications (less than 3 months) were noted in 36 to 61% of cases, and included contralateral weakness, confusion, aphasia, dysarthria, contralateral ataxia, contralateral dystonia, and sensory change. Permanent complications occurred in 14 to 23% of cases, and included aphasia, dysarthria, apraxia, abulia, and death (the latter at 7 days from a pulmonary embolism). Four staged operations were carried out on the second side with good effect on tremor, but with two permanent complications—hypophonia and dysarthria.

Pallidotomy

Adverse effects with pallidotomy are common (10 to 15% incidence of persistent adverse effects with unilateral pallidotomy). The majority of these complications are mild and well tolerated and appear to be far outweighed by the motor benefits of pallidotomy. The initial publications in the 1992-1998 epoch reported that the major complications of pallidotomy were visual field deficits related to lesions encroaching upon the optic tract and facial weakness due to lesions or edema of the capsular fibers for the face. The incidence of these complications appears to have dropped in subsequent studies. The reasons for this are most likely an increased awareness of the potential for this complication and modifications in the surgical technique to optimize the lesion. The most serious complications reported in the 19 papers are intracerebral hematomas related to the penetration of electrodes in the brain. The incidence ranges from 0 to 15% with a mean of approximately 2% (11 of 554 patients). A similar incidence of intracranial hemorrhage is encountered in all functional neurosurgical procedures as reported by centers with a large volume of cases. Several of the patients died. The overall incidence of death from pallidotomy is approximately 0.3%. Other serious reported complications include worsening of cognitive function, most commonly transient post-operative confusion. Neuropsychological evaluations have demonstrated either no or mild deficits, most commonly decreased verbal fluency, particularly after left-sided pallidotomy.

Deep brain stimulation of the Vim nucleus of the thalamus

Complications of implantation of deep brain stimulation electrodes have included subdural hematomas, microhematomas at the tip of the electrode, brain infarcts, seizures, permanent paresthesias, cardiac ischemia, and lead displacement requiring reoperation. As a whole, surgical complications are relatively uncommon and easily managed and rarely result in serious permanent problems.

A common complication of stimulation occurring in most patients is transient (seconds) paresthesias when the stimulator is turned on. Other complications of stimulation that occur infrequently (<10%) are paresis, dysarthria, dysequilibrium, ataxia, dystonia, chorea, persistent paresthesias, and headache. These adverse effects can be reduced or abolished by changing the stimulation parameters. Upon turning off the stimulator, there may be a rebound worsening

of tremor, which prevents patients from turning off the stimulator at night to conserve the battery and reduce tolerance to chronic stimulation.

Device/battery failures have occurred in a few patients. The life of the battery should be 3 to 5 years depending upon the stimulation parameters and whether the stimulation is continuous around the clock or is used just during waking hours. Infection or erosion around the subcutaneous leads may occur.

Deep brain stimulation of the globus pallidus

Transient complications seem common; these include confusion, dysarthria, and hemiparesis, which generally fade in a few weeks. Asymptomatic hemorrhages have been noted on postsurgery magnetic resonance imaging scanning. There are also complications from having the stimulation parameters too high, such as paresthesia, but these are quickly controlled. Long-term complications include increase in speech fluency, dysarthria, and hypophonia, but none of the problems have been severe.

Deep brain stimulation of the subthalamic nucleus

A number of side effects have been reported. In the Grenoble experience, one patient developed a large intracerebral hematoma during surgery with permanent severe paralysis and aphasia. Another developed an infection at the site of the extension lead, requiring removal of the hardware, although she was subsequently reimplanted. Eight of the 20 patients followed for at least 1 year had transient mental status changes after surgery, but these did not last more than 2 weeks. Eighteen patients gained weight, and five developed eyelid-opening apraxia. Mild dystonia can be a consequence of the stimulation, but is accepted by the patients. Several patients reported decreased energy and increased anxiety, and these were thought to be possibly due to the reduction in levodopa dose. A number of complications were also reported by the Toronto group. Two of the patients entered into the study never reached an evaluation point. One, who was slightly cognitively impaired before surgery, became paranoid during surgery and the procedure was discontinued. The other developed an infection of the hardware and it was removed. Of the seven who were evaluated, one had a cortical venous thrombosis with infarction and resultant worsening of hypophonia, one had a decline in verbal memory, one had a personality change, and one had a cognitive decline.

Human fetal mesencephalic transplantation

In cases where long-term immunosuppression occurred, opportunistic pneumonia did occur. Occasional morbidity included confusion, usually transient after surgery, and small hemorrhages near the implantation or needle-track sites.

Subgroups Most Likely to be Harmed:

In general, general cognitive impairment is a predictor of poor outcome to all of the procedures described and patients of advanced age derive decreased benefit.

CONTRAINDICATIONS

CONTRAINDICATIONS

- Significant coexisting medical conditions, psychiatric disease, or focal abnormalities on brain imaging are relative contraindications.
- For deep brain stimulation of the Vim thalamic nucleus, dementia is a relative contraindication because the patient must be able to cooperate in the operating room and because dementia may be exacerbated by any further brain disturbance. Activities in certain occupations may induce the repetitive turning on and off of the device and may contraindicate the procedure.

QUALIFYING STATEMENTS

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This statement is provided as an educational service of the American Academy of Neurology. It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The American Academy of Neurology recognizes that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all of the circumstances involved.

The field is rapidly evolving and the guideline document is based on the published literature up to December 1998.

The procedures require neurosurgeons with a high level of expertise in stereotactic techniques. The majority of reporting centers have multidisciplinary teams of neurosurgeons, neurologists, neurophysiologists, psychiatrists, psychologists, and neuroradiologists with expertise in the diagnosis, assessment, and treatment of movement disorders. The surgical technique is not yet optimized and varies in the different centers; this is one source of variability of results. Inexperienced centers will likely have less favorable results and more adverse side effects.

In general, cognitive impairment is a predictor of poor outcome and patients of advanced age derive decreased benefit. Significant coexisting medical conditions, psychiatric disease, or focal abnormalities on brain imaging are relative contraindications.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness

IOM DOMAIN

Effectiveness
Safety

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Hallett M, Litvan I. Evaluation of surgery for Parkinson's disease: a report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. The Task Force on Surgery for Parkinson's Disease. Neurology 1999 Dec 10;53(9):1910-21. [109 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

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Therapeutics and Technology Assessment Subcommittee

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: A list of American Academy of Neurology (AAN) guidelines, along with a link to a Portable Document Format (PDF) file for this guideline, is available at the AAN Web site.

Print copies: Available from the AAN Member Services Center, (800) 879-1960, or from AAN, 1080 Montreal Avenue, St. Paul, MN 55116.

AVAILABILITY OF COMPANION DOCUMENTS

- Practice statement definitions. St. Paul (MN): American Academy of Neurology.
- Practice statement development. St. Paul (MN): American Academy of Neurology.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on February 12, 2002. The information was verified by the guideline developer as of March 29, 2002.

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